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(71) Applicant *(for all designated States except US)*: NOVO NORDISK A/S [DK/DK]; Novo Allé, DK-2880 Bagsværd (DK).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: SHALMI, Michael [DK/DK]; Edward Falcks Gade 3 2th, DK-1569 København V (DK). KORSGAARD, Niels [DK/DK]; Stormly 18, Hareskovby, DK-3500 Værløse (DK). BAIN, Steven [US/DK]; Stenhøjgårdsvej 58, DK-3460 Birkerød (DK). GULDHAMMER, Birgitte, Hjort [DK/DK]; Elmegårdsallé 71, DK-3400 Hillerød (DK). WEIS, Jan, Ulrik [DK/DK]; Fuglsangvej 6, DK-2830 Virum (DK). HART, Charles, E. [US/US]; 21502 21st Avenue W, Brier, WA 98036 (US).

(74) Common Representative: NOVO NORDISK A/S; Corporate Patents, Novo Allé, DK-2880 Bagsværd (DK).

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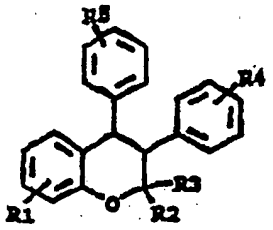
(54) Title: USE OF 3,4-DIPHENYL CHROMANS FOR THE MANUFACTURE OF A PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OR PROPHYLAXIS OF HYPERLIPOPROTEINAEMIA, HYPERTRIGLYCERIDAEMIA, HYPERLIPIDAEMIA OR HYPERCHOLESTEROLAEMIA OR ARTERIOSCLEROSIS OR FOR ANTICOAGULATIVE TREATMENT

(57) Abstract

The present invention provides novel uses of compounds of general formula (I) wherein R1, R4 and R5 are individually hydrogen, hydroxy, halogen, trifluoromethyl, lower alkyl, lower alkoxy or (tertiary amino)(lower alkoxy); and R2 and R3 are individually hydrogen or lower alkyl, or as a pharmaceutically acceptable salt thereof in combination with a pharmaceutically acceptable carrier for the manufacture of a pharmaceutical composition for the treatment or prophylaxis of hyperlipoproteinaemia, hypertriglyceridaemia, hyperlipidaemia or hypercholesterolaemia or arteriosclerosis or for anticoagulative treatment.



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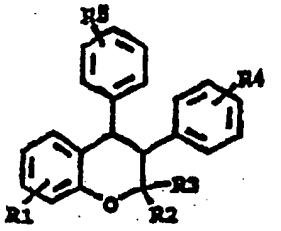
(57) Abstract

The present invention provides novel uses of compounds of general formula (I) wherein R1, R4 and R5 are individually hydrogen, hydroxy, halogen, trifluoromethyl, lower alkyl, lower alkoxy or (tertiary amino)(lower alkoxy); and R2 and R3 are individually hydrogen or lower alkyl, or as a pharmaceutically acceptable salt thereof in combination with a pharmaceutically acceptable carrier for the manufacture of a pharmaceutical composition for the treatment or prophylaxis of hyperlipoproteinaemia, hypertriglyceridaemia, hyperlipidaemia or hypercholesterolaemia or arteriosclerosis or for anticoagulative treatment.



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Use of 3,4-diphenyl chromans for the manufacture of a pharmaceutical composition for the treatment or prophylaxis of hyperlipoproteinaemia, hypertriglyceridaemia, hyperlipidaemia or hypercholesterolaemia or arteriosclerosis or for anticoagulative treatment

FIELD OF THIS INVENTION

The present invention relates to the use of compounds of the general formula I for the treatment of patients suffering from hyperlipoproteinaemia, hypertriglyceridaemia, hyperlipidaemia or hypercholesterolaemia and prophylaxis hereof. The present invention furthermore relates to the use of compounds of the general formula I for the treatment of patients suffering from arteriosclerosis including atherosclerosis and prophylaxis hereof, and furthermore to the use of compounds of the general formula I for the treatment of patients in a need of an anticoagulative treatment or prophylaxis, e.g. following a coronary thrombosis or postoperatively i.e. after surgery. The present invention also embraces pharmaceutical compositions comprising these compounds and methods of using the compounds and their pharmaceutical compositions.

BACKGROUND OF THIS INVENTION

Ischemic heart disease (IHD) the relevant cardiovascular disease in relation to postmenopausal women, primarily is caused by atherosclerosis (Havel and Rapaport, N Eng J Med 1995; 332:1491-1498). Other frequent manifestations of atherosclerosis is cerebrovascular disease, and intermittent claudication. An important risk factor for the development of atherosclerosis is an atherogenic lipid

profile, i.e. hyperlipidaemia with increased LDL-cholesterol and relatively decreased HDL-cholesterol. In epidemiological studies (Samsioe G. Int J Fertil, 1993;38,suppl. 1:19-23) it has been indicated that estrogen therapy in postmenopausal women reduces the stenosis of the coronary arteries, thereby increasing survival rate compared to a non-treated population. An important factor in this effect on the coronary system is a reduction in serum lipids and a normalisation of the relation between LDL-cholesterol and HDL-cholesterol (Samsioe G. Int J Fertil 1994; 39 suppl. 1:43-49).

One object of the present invention is to provide compounds which can effectively be used in the treatment or prophylaxis of hyperlipoproteinaemia, hypertriglyceridaemia, hyperlipidaemia or hypercholesterolaemia.

Data on men suggest that a 35% reduction in LDL-cholesterol is required to achieve a 50% reduction in cardiovascular disease, i.e. coronary atherosclerosis provided that LDL-cholesterol reduction are the sole cause of cardioprotection. However, estrogens reduce LDL-cholesterols by only 5-10%. It is therefore now believed that the lipid effects account for only 25-40% of the reduction in the incidence of coronary heart disease after estrogen replacement therapy. A possible mechanism could be a direct effect on the vessel wall improving blood flow and inhibiting the atherogenic mechanisms independent on an effect on plasma lipids.

Another object of the present invention is to provide compounds which can effectively be used in the treatment or prophylaxis of arteriosclerosis including atherosclerosis.

Coagulation and thrombosis are important mechanisms involved in the pathogenesis of atherosclerosis and its complications such as vascular occlusion and embolism. Furthermore, blood clotting is important for the development of vascular restenosis following surgical intervention of

blocked arteries. Restenosis occurs in about 35% of the patients after 6 months. Current therapy such as heparin , low molecular heparin and aspirin or stents have failed to reduce the incidence of restenosis. New therapeutic possibilities which can inhibit a tendency for thrombosis after endothelial damage are therefore needed.

Another further object of the present invention is to provide compounds which can effectively be used in the treatment or prophylaxis of patients in a need of an anticoagulative treatment or prophylaxis, e.g. following a coronary thrombosis or after surgery.

Recent studies (Writing group for the PEPI trial, JAMA 273:199, 1995) confirm that oral estrogen taken alone or in combination with medroxy-progesterone acetate or micronized progesterone is associated with a beneficial effect on the risk of developing cardiovascular disease through an improved effect on lipoprotein and the fibrinogen profile. However, estrogen is also known to have adverse effects on endometrium and perhaps breast tissue by increasing the frequency of malignancies in these areas after prolonged treatment.

Thus, there is a need for new compounds which have beneficial effects on hyperlipoproteinaemia, hypertriglyceridaemia, hyperlipidaemia or hypercholesterolaemia or arteriosclerosis including atherosclerosis or as an anticoagulant, but without introducing significant effects in the reproductive tissues.

Centchroman is a non-steroidal compound known to have antiestrogenic activity. It is in use in India as an oral contraceptive (see, for example, Salman et al., U.S. Patent Specification No. 4,447,622; Singh et al., Acta Endocrinal (Copenh) 126 (1992), 444 - 450; Grubb, Curr Opin Obstet Gynecol 3 (1991), 491 - 495; Sankaran et al., Contraception 9 (1974), 279 - 289; Indian Patent Specification No. 129187). Centchro-

man has also been investigated as an anti-cancer agent for treatment of advanced breast cancer (Misra et al., Int J Cancer 43 (1989), 781 - 783). Recently, centchroman as a racemate has been found potent as a cholesterol lowering pharmaceutical expressed by a significant decrease of the serum concentrations (S.D. Bain et al., J Min Bon Res 9 (1994), S 394).

U.S. patent 5,280,040 describes methods and pharmaceutical compositions for reducing bone loss using 3,4-diarylchromans and their pharmaceutically acceptable salts.

BRIEF DESCRIPTION OF THIS INVENTION

It has, surprisingly, been found that compounds of the general formula I as stated in claim 1 can be used in the treatment or prophylaxis of hyperlipoproteinaemia, hypertriglyceridaemia, hyperlipidaemia or hypercholesterolaemia and furthermore it has also, surprisingly, been found that compounds of the general formula I as stated in Claim 2 and 3 can be used in the treatment or prophylaxis of arteriosclerosis including atherosclerosis and that compounds of the general formula I as stated in claim 4 can be used in the treatment or prophylaxis of patients in a need of an anticoagulative treatment or prophylaxis, e.g. following a coronary thrombosis or after surgery.

DETAILED DESCRIPTION OF THIS INVENTION

The present invention is based in part on the discovery that a representative 3,4-diarylchroman, centchroman (3,4-trans-2,2-dimethyl-3-phenyl-4-[p-(beta-pyrrolidinoethoxy)phenyl]-7-methoxychroman) is effective as a hypolipoproteinaemic, hypotriglyceridaemic, hypolipidaemic or hypocholesterolaemic compound, inter alia in rabbits fed with cholesterol containing diet. These animal models are generally recognized models of hyperli-

poproteinaemia, hypertriglyceridaemia, hyperlipidaemia or hypercholesterolaemia. These data thus indicate that the 3,4-diarylchromans are useful as therapeutive and preventive hypolipoproteinaemic, hypotriglyceridaemic, hypolipidaemic or hypocholesterolaemic agents in mammals, including primates such as humans.

Furthermore, the present invention is based in part on the discovery that a representative 3,4-diarylchroman, centchroman (3,4-trans-2,2-dimethyl-3-phenyl-4-[p-(beta-pyrrolidinoethoxy)phenyl]-7-methoxychroman) is also effective against the direct vascular effects of arteriosclerosis including atherosclerosis, inter alia in rabbits fed with cholesterol containing diet. These animal models are generally recognized models of arteriosclerosis including atherosclerosis. These data thus indicate that the 3,4-diarylchromans are useful as therapeutic agents against arteriosclerosis including atherosclerosis in mammals, including primates such as humans.

The present invention is yet further based in part on the discovery that a representative 3,4-diarylchroman, centchroman (3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-(pyrrolidin-1-yl)ethoxy)phenyl]-7-methoxychroman) has preventive or therapeutic anticoagulative activities when administered inter alia to rats. These animal models are generally recognized models of patients in a need of an anticoagulative treatment or prophylaxis, e.g. following a coronary thrombosis or after surgery. These data thus indicate that the 3,4-diarylchromans of formula I are useful as therapeutic and preventive agents to mammals, including primates such as humans, in a need of an anticoagulative treatment or prophylaxis, e.g. following a coronary thrombosis or after surgery.

This invention is related to the treatment or prophylaxis of disorders as defined in the Lipid Research Clinics Program. J.A.M.A. 251 (1984), 351-364 and J.A.M.A. 251 (1984), 365 - 374 or what a person skilled

in the art may consider as subject for treatment or prophylaxis.

Within the present invention, compounds of formula I are used for the indications as stated in claims 1-4 in a patient. Within formula I, R1, R4 and R5 are individually hydrogen, halogen, trifluoromethyl, lower alkyl, lower alkoxy or (tertiary amino)(lower alkoxy); and R2 and R3 are individually hydrogen or a lower alkyl. As used herein, the term "lower alkyl" includes straight and branched chain alkyl radicals containing from 1 to 6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, n-amyl, sec-amyl, n-hexyl, 2-ethylbutyl, 2,3-dimethylbutyl and the like. The term "lower alkoxy" includes straight and branched chain alkoxy radicals containing from 1 to 6 carbon atoms, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy, n-amyloxy, sec-amyloxy, n-hexyloxy, 2-ethylbutoxy, 2,3-dimethylbutoxy and the like. "Halogen" includes chloro, fluoro, bromo and iodo. The tertiary amino radical may be a N,N-dialkylamine such as a N,N-dimethylamino, N,N-diethylamino, N,N-dipropylamino and N,N-dibutylamino or a polymethyleneimine, e.g., piperidine, pyrrolidine, N-methylpiperazine or morpholine. Herein, the term "(tertiary amino)(lower alkoxy)" is a lower alkoxy group which is substituted by a tertiary amino group. Preferred compounds include those in which R^1 is lower alkoxy; R^2 and R^3 are lower alkyl, especially methyl; R^4 is hydrogen; and R^5 is (tertiary amino)(lower alkoxy) of the polymethyleneimine type. Within particularly preferred embodiments, R^1 is in the 7-position and is lower alkoxy, particularly methoxy; each of R^2 and R^3 is methyl, R^4 is hydrogen, and R^5 is in the 4-position and is a (tertiary amino)(lower alkoxy) radical such as 2-(pyrrolidin-1-yl)ethoxy. To be included by this invention are all pharmaceutically acceptable salts of the mentioned compounds of formula I.

It is preferred to use the compounds of formula I in the transconfiguration. These compounds may be used as racemic mixtures, or the isolated stereoisomers e.g. d- or l- enantiomers, may be used. The trans-l-en-

antiomers are more preferred.

A particularly preferred compound for use within the present invention is centchroman having the formula IV as stated in claim 14.

Although only one enantiomer is shown, it will be understood that the formula IV is used herein to designate the transconfiguration of the 3- and 4-phenyl groups and that both the d- and l-enantiomers, as well as the racemic mixture are included.

3,4-diarylchromans are prepared according to known methods, such as those disclosed in U.S. Patent Specification No. 3,340,276 to Carney et al., U.S. Patent Specification No. 3,822,287 to Bolger, and Ray et al., J Med Chem 19 (1976), 276 - 279, the contents of which are incorporated herein by reference. Conversion of the cis isomer to the trans configuration by means of an organometallic base-catalyzed rearrangement is disclosed in U.S. Patent Specification No. 3,822,287. The optically active d- and l-enantiomers may be prepared as disclosed by Salman et al. in U.S. Patent Specification No. 4,447,622 (incorporated herein by reference) by forming an optically active acid salt which is subjected to alkaline hydrolysis to produce the desired enantiomer. If R^2 is different from R^3 and R^4 is different from R^5, the general formula I covers 8 optical isomers.

Within the present invention, 3,4-diarylchromans may be prepared in the form of pharmaceutically acceptable salts, especially acid-addition salts, including salts of organic acids and mineral acids. Examples of such salts include salts of organic acids such as formic acid, acetic acid, propionic acid, fumaric acid, glycolic acid, lactic acid, pyruvic acid, oxalic acid, succinic acid, malic acid, tartaric acid, citric acid, benzoic acid, salicylic acid and the like. Suitable inorganic acid-addition salts include salts of hydrochloric, hydrobromic, sulphuric and phosphoric acids and the like.

The acid addition salts may be obtained as the direct products of compound synthesis. In the alternative, the free base may be dissolved in a suitable solvent containing the appropriate acid, and the salt isolated by evaporating the solvent or otherwise separating the salt and solvent.

3,4-diarylchromans and their salts are useful within human and veterinary medicine, for example, in the treatment or prevention of patients suffering from hyperlipoproteinaemia, hypertriglyceridaemia, hyperlipidaemia or hypercholesterolaemia or arteriosclerosis including atherosclerosis or in need of anticoagulative treatment or prophylaxis e.g. following a coronary thrombosis or after surgery. For use within the present invention, 3,4-diarylchromans and their pharmaceutically acceptable salts are formulated with a pharmaceutically acceptable carrier to provide a medicament for parenteral, oral, nasal, rectal, subdermal or intradermal or transdermal administration according to conventional methods. Formulations may further include one or more diluents, fillers, emulsifiers, preservatives, buffers, excipients, etc. and may be provided in such forms as liquids, powders, emulsions, suppositories, liposomes, transdermal patches, controlled release, dermal implants, tablets, etc. One skilled in this art may formulate the compounds in an appropriate manner, and in accordance with accepted practices, such as those disclosed in Remington's Pharmaceutical Sciences, Gennaro, ed., Mack Publishing Co., Easton, PA, 1990.

Oral administration is preferred. Thus, the active compound is prepared in a form suitable for oral administration, such as a tablet or capsule. Typically, a pharmaceutically acceptable salt of the compound is combined with a carrier and moulded into a tablet. Suitable carriers in this regard include starch, sugars, dicalcium phosphate, calcium stearate, magnesium stearate and the like. Such compositions may further include one or more auxiliary substances, such as wetting agents, emulsifiers, preservatives, stabilizers, colouring additives, etc.

Pharmaceutical compositions containing a compound of formula I may be administered one or more times per day or week. An effective amount of such a pharmaceutical composition is the amount that provides a clinically significant effect as hypolipoproteinaemic, hypotriglyceridaemic, hypolipidaemic or hypocholesterolaemic agents or a clinically significant effect against arteriosclerosis including atherosclerosis or provides a clinically significant effect to patients in a need of an anticoagulative treatment or prophylaxis e.g. following a coronary thrombosis or after surgery. Such amounts will depend, in part, on the particular condition to be treated, age, weight, and general health of the patient, and other factors evident to those skilled in the art.

The pharmaceutical compositions containing a compound of formula I may be administered in unit dosage form one or more times per day or week. In the alternative, they may be provided as controlled release formulations suitable for dermal implantation. Implants are formulated to provide release of active compound over the desired period of time, which can be up to several years. Controlled-release formulations are disclosed by, for example, Sanders et al., J Pharm Sci 73 (1964), 1294 - 1297, 1984; U.S. Patent Specification No. 4,489,056; and U.S. Patent Specification No. 4,210,644, which are incorporated herein by reference.

The following examples are offered by way of illustration, not limitation.

Examples of preferred compounds of formula I are centchroman as a racemic mixture and as l-centchroman and d-centchroman. Furthermore, 3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-(pyrrolidin-1-yl)ethoxy)phenyl]-7-hydroxychroman is a preferred compound. The more preferred compound is trans-l-centchroman (l-3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-7-methoxychroman).

Examples of pharmaceutically acceptable acid addition salts are salts with non-toxic acids, either inorganic acids such as hydrochloric acid, sulphuric acid and phosphoric acid, or organic acids such as formic acid, acetic acid, propionic acid, succinic acid, fumaric acid, glyconic acid, lactic acid, citric acid, ascorbic acid, benzoic acid, embonic acid, methanesulphonic acid and malonic acid.

The present invention is further illustrated by the following examples which, however, are not to be construed as limiting the scope of protection. The features disclosed in the foregoing description and in the following examples may, both separately and in any combination thereof, be material for realising the invention in diverse forms thereof.

EXAMPLE 1

The effects of l-centchroman on plasma cholesterol have been investigated in both rats and rabbits.

In the first study sham surgery or ovariectomy (OVX) was performed on 56 female Sprague-Dawley rats and the animals were assigned to the following treatments (8 rats per group): 1) sham/vehicle; 2) OVX/vehicle, 3) OVX/ethynyl estradiol 0.2 mg/kg; 4) OVX/l-centchroman 1 mg/kg; 5) OVX/l-centchroman 5 mg/kg; 6) OVX/l-centchroman 10 mg/kg;7) OVX/l-centchroman 25 mg/kg. The doses were administered three times per week for 5 weeks by oral gavage. At the conclusion of the experiment serum was collected for determination of cholesterol level (US patent 5,407,955).

l-centchroman had a marked effect on serum cholesterol in all doses and reduced the cholesterol level even below the level of the sham operated animals (Table 1).

Table 1. Effect of l-centchroman on serum cholesterol in rats

Treatment	Serum cholesterol (mmol/l)
Sham/vehicle	2.2 ± 0.3
OVX/vehicle	2.9 ± 0.3
OVX/ethynyl estradiol 0.2 mg/kg	1.9 ± 0.4
OVX/l-centchroman 1 mg/kg	1.4 ± 0.3*
OVX/l-centchroman 5 mg/kg	1.5 ± 0.4
OVX/l-centchroman 10 mg/kg	1.5 ± 0.2
OVX/l-centchroman 25 mg/kg	1.2 ± 0.2*

Values are mean ± SD. * indicate significant reduction of serum cholesterol compared to OVX rats treated with ethynyl estradiol; $p < 0.002$.

In order to show a clear dose-response effect on serum cholesterol a further study was performed with l-centchroman.

Again sham surgery or ovariectomy was performed on 56 female rats and the rats were assigned to the following treatments: 1) sham/vehicle; 2) OVX/vehicle, 3) OVX/ethynyl estradiol 0.2 mg/kg; 4) OVX/l-centchroman 0.05 mg/kg; 5) OVX/l-centchroman 0.1 mg/kg; 6) OVX/l-centchroman 0.5mg/kg;7) OVX/l-centchroman 1 mg/kg. The doses were administered three times per week for 5 weeks by oral gavage. At the conclusion of the experiment serum was collected for determination of cholesterol level (US patent 5,407,955). In this experiment serum cholesterol was reduced in a dose-dependent manner (table 2).

Table 2. Effect of l-centchroman on serum cholesterol in rats

Treatment	Serum cholesterol (mmol/l)
Sham/vehicle	2.1 ± 0.3
OVX/vehicle	2.7 ± 0.3
OVX/ethynyl estradiol 0.2 mg/kg	1.6 ± 0.4
OVX/l-centchroman 0.05 mg/kg	2.4 ± 0.4
OVX/l-centchroman 0.1 mg/kg	2.3 ± 0.3
OVX/l-centchroman 0.5 mg/kg	1.7 ± 0.3*
OVX/l-centchroman 1.0 mg/kg	1.5 ± 0.4*

Values are mean ± SD. * indicate significant reduction of serum cholesterol compared to sham/vehicle treated animals; $p<0.003$.

The effects of l-centchroman on plasma lipids were also investigated in cholesterol fed rabbits. One week before the experiment was started 30 sexually mature New Zealand White rabbits were ovariectomized during pentobarbital anaesthesia. Following recovery subcutaneous treatment was started in three groups: Vehicle, 17-ß-estradiol or l-centchroman 7.5 mg/kg. The doses were administered three times per week for 4 weeks. At the end of the experiment plasma samples for analysis of serum cholesterol were taken. As shown in table 3 l-centchroman reduced serum cholesterol significantly compared to the level in vehicle treated animals and estrogen treated animals.

Table 3. Effect of l-centchroman on serum cholesterol in ovariectomized rabbits

Treatment	Serum cholesterol (mmol/l)
OVX/vehicle	11.0 ± 1.1
OVX/17-ß-estradiol 50 µg/kg 3x/week	7.5 ± 0.5*
OVX/l-centchroman 7.5 mg/kg 3x/week	8.2 ± 0.7*

Values are mean ± SEM. * indicate significant reduction of serum cholesterol compared to OVX/vehicle treated animals; $p<0.05$.

EXAMPLE 2

The effects of I-centchroman on the acummulation of lipid into the aortic wall i.e. a central mechanism in the atherogenic process was investigated in New Zealand White rabbits. One week before the experiment was started 45 sexually mature New Zealand White female rabbits were ovariectomized during pentobarbital anaesthesia. Additionally a group of 45 age and weight matched male rabbits were included in the experiment. Following recovery oral treatment was commenced. Males and females were treated in 3 groups (15 animals per group): 1) Placebo treated animals; 2) 17-ß-estradiol 2.5 mg/kg /day; 2) I-centchroman, 2.5 mg/kg/day. After 14 days of treatment cholesterol was added to the food. Every second day a blood sample was collected from each rabbit and the total serum cholesterol was determined. (Holm P et al. Atherosclerosis 115:191, 1995). On basis of this measurement the cholesterol concentration in the feeding was regulated on the following days until next measurement. In that way serum cholesterol was kept constant throughout the treatment period even though some of the treatments are known to have effects on plasma cholesterol level. The direct effect of treatment on the vessel wall could then be isolated. After 3 months of treatment the animals were killed, the aorta from each animal was isolated and the cholesterol accumulated within the intima of the aorta was determined. (Holm P et al Atherosclerosis, 115:191, 1995).

The results are shown in table 4. It is clearly seen that both estrogen and I-centchroman in both male and female rabbits had a significant reducing effect on the intimal cholesterol content, which is independent of the serum cholesterol since this was kept constant throughout the

experiment. The anti-atherosclerotic effect of l-centchroman may therefore partly be due to a direct vascular wall effect.

Table 4. Effect of l-centchroman and estrogen on intimal cholesterol content

Treatment	Intimal cholesterol (mmol/l) Female	Intimal cholesterol (mmol/l) Male
Placebo	45 ± 9	27 ± 5
17-ß-estradiol	8 ± 3*	8 ± 2*
l-centchroman 2.5 mg/kg	18 ± 5*	13 ± 4*

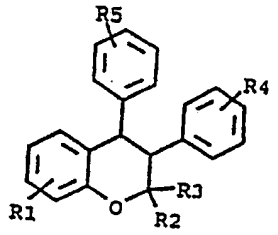
Values are mean ± SEM. * indicate significant reduction of intimal cholesterol compared to placebo treated animals; $p<0.05$.

EXAMPLE 3

In vitro it has been shown that l-centchroman in rabbit platelet-rich plasma inhibited platelet aggregation induced by platelet activating factor (PAF). EC50 for this effect was between 3 and 10 µg/ml. ADP-induced aggregation was not affected.

CLAIMS

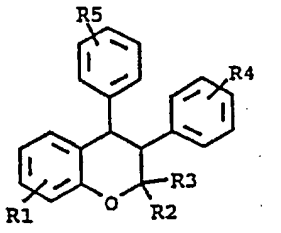
1. The use of compounds of the general formula I



(I)

wherein R1, R4 and R5 are individually hydrogen, hydroxy, halogen, trifluoromethyl, lower alkyl, lower alkoxy or (tertiary amino)(lower alkoxy); and R2 and R3 are individually hydrogen or lower alkyl, or as a pharmaceutically acceptable salt thereof in combination with a pharmaceutically acceptable carrier for the manufacture of a pharmaceutical composition for the treatment or prophylaxis of hyperlipoproteinaemia, hypertriglyceridaemia, hyperlipidaemia or hypercholesterolaemia with the proviso that the pertinent compounds and the pharmaceutical compositions as defined do not include the optic isomer d-centchroman.

2. The use of compounds of the general formula I

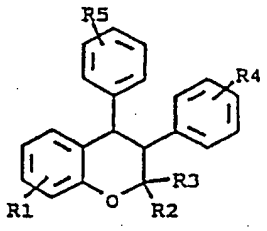


(I)

wherein R1, R4 and R5 are individually hydrogen, hydroxy, halogen, trifluoromethyl, lower alkyl, lower alkoxy or (tertiary amino)(lower alkoxy); and R2 and R3 are individually hydrogen or lower alkyl, or as a pharmaceutically acceptable salt thereof in combination with a pharmaceutically acceptable carrier for the manufacture of a pharmaceutical composition for the treatment or prophylaxis of arteriosclerosis including atherosclerosis.

3. The use according to claim 2 for the treatment or prophylaxis of atherosclerosis.

4. The use of compounds of the general formula I



(I)

wherein R^1, R^4 and R^5 are individually hydrogen, hydroxy, halogen, trifluoromethyl, lower alkyl, lower alkoxy or (tertiary amino)(lower alkoxy); and R^2 and R^3 are individually hydrogen or lower alkyl, or as a pharmaceutically acceptable salt thereof in combination with a pharmaceutically acceptable carrier for the manufacture of a pharmaceutical composition for the treatment or prophylaxis of patients in a need of an anticoagulative treatment or prophylaxis, e.g. following a coronary thrombosis or after surgery.

5. The use according to any one of claims 1-4, wherein R1 in the compound used is lower alkoxy, R2 and R3 are lower alkyl, R4 is hydrogen and R5 is tertiary amino lower alkoxy.

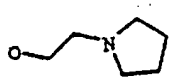
6. The use according to any one of claims 1-5, wherein R1 is methoxy.

7. The use according to any one of claims 1-6 wherein R2 is methyl.

8. The use according to any one of claims 1-7 wherein R3 is methyl.

9. The use according to any one of claims 1-8 wherein R4 is hydrogen.

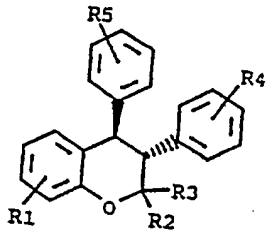
10. The use according to any one of claims 1-9 wherein R5 is a group as stated in formula II below:



(II)

11. The use according to any one of claims 1-10 wherein said compound is stereoisomer including an isolated d- or l-enantiomer.

12. The use according to any one of claims 1-11 wherein said compound has the general formula III as stated below:

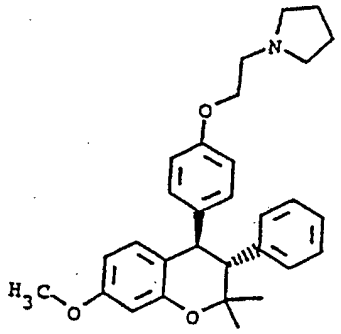


(III)

wherein R^1, R^2, R^3, R^4 and R^5 each has the meaning as stated in any of the preceding claims.

13. The use according to anyone of the preceding claims wherein said compound is an isolated l-enantiomer.

14. The use according to any one of claims 1-4 wherein said compound is centchroman 3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-(pyrrolidin-1-yl)ethoxy)phenyl]-7-methoxychroman having the formula IV as stated below:



(IV)

15. The use according to claim 14 wherein said compound is an isolated d- or l-enantiomer.

16. The use according to claim 14 wherein said compound is an

isolated l-enantiomer.

17. The use according to any one of the preceding claims wherein said composition is in a form suitable for oral administration.

18. The use according to any one of the preceding claims wherein said compound is administered as a dose in a range from about 0.001 to 75, preferably in a range from about 0.01 to 75, more preferably in the range from about 0.01 to 50 and especially in the range from about 0.1 to 25 mg/kg patient per day.

19. The use according to any one of the preceding claims wherein said composition is administered one or more times per day or week.

20. The use according to any one of the preceding claims wherein said composition is in the form of a dermal implant.

21. Method for treatment and prophylaxis of hyperlipoproteinaemia, hypertriglyceridaemia, hyperlipidaemia or hypercholesterolaemia comprising administering to a patient a clinically effective amount of a compound of formula I as stated in claim 1 stated to be used in any of the preceding use claims, or a pharmaceutically acceptable salt thereof in a sufficiently therapeutic and preventive amount as a hypolipoproteinaemic, hypotriglyceridaemic, hypolipidaemic or hypocholesterolaemic agent.

22. Method for treatment and prophylaxis of arteriosclerosis including atherosclerosis comprising administering to a patient a clinically effective amount of a compound of formula I as stated in claim 2, stated to be used in any of the preceding use claims, or a pharmaceutically acceptable salt thereof in an amount sufficient to treat or prevent arteriosclerosis including atherosclerosis.

23. Method for the anticoagulative treatment and prophylaxis of patients comprising administering to a patient a clinically effective amount of a compound of formula I as stated in claim 4, stated to be used in any of the preceding use claims, or a pharmaceutically acceptable salt thereof in an amount sufficient to anticoagulate patients, e.g. following a coronary thrombosis or after surgery.

24. Method of treating or preventing hyperlipoproteinaemia, hypertriglyceridaemia, hyperlipidaemia or hypercholesterolaemia which method comprises administering a clinically effective amount of a compound of formula I or a salt thereof and pharmaceutically acceptable compositions, according to previous claims to a patient in need of such a treatment or prophylaxis.

25. Method of treating or preventing arteriosclerosis including atherosclerosis which method comprises administering a clinically effective amount of a compound of formula I or a salt thereof and pharmaceutically acceptable compositions, according to previous claims to a patient in need of such a treatment or prophylaxis.

26. Method for the anticoagulative treatment or prophylaxis of patients, e.g. following a coronary thrombosis or after surgery, which method comprises administering a clinically effective amount of a compound of formula I or a salt thereof and pharmaceutically acceptable compositions containing such a compound according to previous claims to a patient in need of such a treatment or prophylaxis.

27. Any novel feature or combination of features described herein.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 96/00014

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 31/40, A61K 31/35
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 1103094 A (E. MERCK AKTIENGESELLSCHAFT), 14 February 1968 (14.02.68), page 1, line 38 --	1-3,4-20
X	Chemical Abstracts, Volume 105, No 13, 29 Sept 1986 (29.09.86), (Columbus, Ohio, USA), Srivastava, R. et al, "Prostanoid mediated effects of centchroman, a non-steroidal oral contraceptive", page 94, THE ABSTRACT No 108751w, Agents Actions 1986, 18 (5-6), 596-599 --	4-20
P,X	EP 0672412 A2 (ELI LILLY AND COMPANY), 20 Sept 1995 (20.09.95) -- ----------	1-20

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 March 1996	29 - 04 - 1996
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 96/00014

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 21-26
because they relate to subject matter not required to be searched by this Authority, namely:
A method for treatment of the human or animal body by therapy, see rule 39.1.

2. [X] Claims Nos.: 27
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claim 27 is obscure and does not clearly define the matter for which protection is sought, see Article 6.

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/DK 96/00014

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB-A- 1103094	14/02/68	BE-A- 694025	14/08/67
		CH-A- 494222	31/07/70
		DE-A- 1543749	11/12/69
		FR-M- 6192	22/07/68
		NL-A- 6702140	17/08/67
		US-A- 3535344	20/10/70
EP-A2- 0672412	20/09/95	NONE	